REMARKS

Upon entry of the above amendments, claims 12-39, 58-73 will be pending. Claims 12 and 65 are amended to correct inadvertent typographical errors. Applicants reserve the right to pursue subject matter that will no longer be pending after the amendment above, or which has not yet been pursued, in a related application. The claim amendments add no new matter as there is basis in the specification throughout, for example, in the claims as filed.

Applicants respectfully request consideration of the pending claims.

Claim Rejections – 35 USC Section 112

Applicants thank the Examiner for withdrawing the rejections of claims 12-39 and 58-73 under 35 USC Section 112.

Claim Rejections – 35 USC Section 102

Applicants thank the Examiner for withdrawing the rejections of claims 13-22, 24, 58, and 69-73 under 35 USC Section 102.

Double Patenting

Claims 1-39 and 58-73 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application Number 10/933,611. As this rejection is a provisional rejection, Applicants will await the notice that one of the sets of claims is allowable, and will file any terminal disclaimer, if appropriate, at that time.

Claim Objections

Claims 12 and 65 were objected to because of the following informalities: The Examiner stated that it appears that step f) in claim 12 should refer to the identified different fragments in step e (as opposed to step a). Also, step f) in claim 65 should refer to step d). Applicants thank the Examiner for pointing out this inadvertent error, and have amended the claims as suggested.

Claim Rejections 35 USC Section 103

Claims 12-22, 24, 26-32, 34-39, and 58-73 were rejected under 35 USC 103(a) as unpatentable over Zabeau et al (WO 00/66771) in view of Little et al (1997, reference A255 on the IDS submitted 4/18/2006).

The Examiner stated that with regard to claims 12, 29, 35, 59, and 65, Zabeau teaches a method comprising

a) cleaving the target nucleic acid molecule into fragments by contacting the target nucleic acid molecule with one or more specific cleavage reagents;

b) cleaving or simulating cleavage of a reference nucleic acid molecule into fragments using the same cleavage reagent(s;

c) determining mass signals of the fragments produced in a) and b);

d) determining differences in the mass signals between the fragments produced in a) and the fragments produced in a) and b);

e) identifying fragments that are different between the target nucleic acid and the reference nucleic acid;

g) determining a reduced set of sequence variation candidates from the differences in the mass signals and thereby determining sequence variations in the target compared to the reference biomolecule.

The Examiner noted that "Zabeau does not teach determining compomers corresponding to the identified different fragments that are compomer witnesses (step f, claim 12; step e, claim 29; step f, claim 35; step 3, claim 59; step f, claim 65)." The Examiner cites the Little reference as teaching "determining compomers corresponding to different fragments that are compomer witnesses." The Examiner states that

> when Little measures the masses of ...fragments (in this case, primer extension products), and from these masses deduces a specific allele of apolipoprotein E that is present, he determines a compomer (he correlates the observed mass with a

> specific primer extension product, and thus necessarily also correlates the mass with a specific base composition, i.e. a compomer). Since this compomer has a predicted mass which differs by a value (which is neither explicitly defined in the specification nor recited in the claim and thus can be any value) that is less than or equal to a sufficiently small mass difference from the actual observed mass of the fragment, this compomer is also a witness compomer. Thus this limitation can be interpreted to be nothing more than inferring the sequence of a fragment of a nucleic acid based on its mass.
>
> The Examiner further stated that it
>
> would have been prima facie obvious to one of ordinary skill in the art at the time the invention of the instant application was made to infer the sequence of the nucleic acids based on their observed masses (as was done by Little) when practicing the method of Zabeau, in order to obtain the benefit of deriving sequence information for diagnostic purposes such as the genotyping of apolipoprotein E performed by Little, who states: 'Clearly apolipoprotein E is an important protein to follow in laboratory medicine' (last sentence, first paragraph of introduction, page 545).

Applicants respectfully traverse this rejection. As stated in the September 8, 2006 Amendment, the Zabeau reference does not provide any motivation to combine the Zabeau teachings with the use of compositional isomers. In fact, Zabeau mentions compositional isomers in the background section of the application, and distinguishes the use of prior art methods that obtain these compositional isomers by stating:

> Some of the MS-based assays have been used for the scoring of defined mutations or polymorphisms. Other processes derive multiple oligonucleotide fragments and yield a "mass-fingerprint" so as to analyze a larger target nucleic acid region for mutation and/or polymorphism. The latter MS analyses are however considerably less informative in that they are essentially restricted to the detection of sequence variations. *The methods cannot be applied to diagnostic sequencing of nucleic acids, where the term diagnostic sequencing means the unequivocal determination of the presence, the nature and the position of sequence variations.* **At best, the measurements confirm the base composition of small fragments whose masses are determined with sufficient accuracy to reduce the number of possible compositional isomers.** Also, it will be realized that only certain changes in composition (as revealed by shifts in the mass spectrum) can be unambiguously assigned to a polymorphism or mutation. (Zabeau, page 4, ll. 10-22, lines cited in an earlier Office Action in bold, emphasis added in italics).

Zabeau states that these prior art MS analyses cannot be applied to diagnostic sequencing because they do not unequivocally determine "the presence, the nature and the position of sequence variations," and "at best" only reduce the number of possible compositional isomers. The present invention, in contrast, does provide methods involving the use of compositional isomers to reduce the number of sequence variations to analyze; these methods do result in the determination of the presence, nature, and position of sequence variations. In this passage, however, Zabeau characterizes methods that "at best" reduce the number of compositional isomers as not being sufficient to determine the presence, the nature and the position of sequence variations." Thus, one of ordinary skill in the art would have no motivation to combine Zabeau's method with a method for reducing the number of possible compositional isomers.

One of the "prior art" references that Zabeau cites in this passage is WO98/20166, titled "DNA Diagnostics Based on Mass Spectrometry" (cited in Zabeau at page 4, line 7), in which all of the authors of the Little reference are listed as inventors. The reference discusses the use of a PROBE method, in which the masses of fragments (primer extension products) are measured. In Example 12, of the reference, at page 145, line 10-pag 148, line 2, a PROBE method is used to determine an apolipoprotein E, by measuring the masses of the primer extension products. Thus, Zabeau already recognized the particular teachings of the Little reference that the Examiner cited, the comparison of the masses of primer extension products in order to determine an apolipoprotein E allele. Not only did Zabeau cite to the WO98/20166 reference, Zabeau distinguished its method. The use of compomers, or compomer witnesses is not mentioned in any other section of the Zabeau reference. Thus, Zabeau does not only not motivate one of ordinary skill in the art to seek out teachings on compomer witnesses, Zabeau distinguishes these sort of teachings.

Little discusses the use of PROBE, which involves mass spectrometric analysis of primer extension products. These primer extension products may then be compared with each other. Little does not discuss a cleavage analysis such as that discussed in the Zabeau reference. Thus, not only does the Zabeau reference not motivate one of ordinary skill in the art to seek out teachings regarding compomer witnesses, the Little reference is not analogous as it is not within the same field of fragmentation analysis, but instead involves the analysis of primer extension products.

Further, the Examiner states that Zabeau teaches a method comprising steps a-e of claim 12, as well as step g. Without addressing steps a-e, Applicants, however, respectfully disagree with the Examiner's analysis of step g). Step g) of claim 12 requires "determining a reduced set of sequence variations corresponding to the compomer witnesses that are candidate sequences to determine the sequence variations in the target nucleic acid compared to the reference nucleic acid." The Examiner states that in Zabeau, "the detection of a mass necessarily defines a reduced set of sequence variation candidates, i.e. the set of all possible sequences is reduced to the set of all possible sequences having that particular mass." But, as Zabeau does not determine a reduced set of sequence variations corresponding to the compomer witnesses, this is not the same procedure as step g) of claim 12. In fact, Zabeau discusses comparing the "mass spectra of the one or more target nucleic acids" with the "mass spectra of the reference nucleic acid sequence" by *"systematic computational analysis."* (page 7, lines 13-21, emphasis added). Thus, rather than limiting the analysis to a reduced set of sequence variations, it appears from Zabeau that systematic computational analysis is used to compare the "products of the cleavage reactions" that is, more than just the reduced set of fragments that correspond to compomer witnesses.

Applicants therefore respectfully request that the rejection of claims 12-22, 24, 26-32, 34-39, and 58-73 under 35 USC Section 103 be withdrawn.

Claims 23 and 33 were rejected under 35 USC Section 103(a) as being unpatentable over Zabeau in view of Little, as applied to claims 12-22, 24, 26-32, 34-39, and 58-73, and further in view of McCarthy et al (WO 97/03210). The Examiner states that the Zabeau and Little references do not teach using DNA glycosylase to cleave the nucleic acid, and that "McCarthy teaches a method of achieving base-specific cleavage by introducing a modified base that is a substrate for a DNA glycosylase, excising the modified base using the DNA glycosylase to generate abasic sites, cleaving the phosphate linkages at the abasic sites, and analyzing the cleavage products produced." The Examiner noted: "McCarthy does not teach analyzing the cleavage products using mass spectrometry."

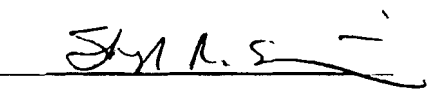
Applicants respectfully request that the Examiner withdraw the rejection of claims 23 and 33, for the reasons discussed above as applied to claims 12-22, 24, 26-32, 34-39, and 58-73.

Claim 25 was rejected under 35 USC 103(a) as unpatentable over Zabeau in view of Little and further in view of Muller. The Examiner states that Zabeau and Little do not teach analysis of epigenetic changes in a nucleic acid, and Muller teaches the use of a mass-spectrometry-based method for analyzing the imprinting status of the TSSC3 gene...Muller does not teach a method involving base-specific cleavage of a target nucleic acid (but rather a target-dependent primer extension, like Little)." Applicants respectfully request that the Examiner withdraw the rejection of claims 23 and 33, for the reasons discussed above as applied to claims 12-22, 24, 26-32, 34-39, and 58-73. Applicants further respectfully disagree with the Examiner's substitution of the Zabeau method for the Muller method for analyzing epigenetic alterations, as there is no motivation in Zabeau for this combination.

CONCLUSION

Applicants respectfully submit that, after entry of the amendment above, all pending claims will be in condition for allowance, and they earnestly solicit an early notice to such effect. That said, should any issues or questions remain, the Examiner is encouraged to telephone the undersigned at (760) 473-9472 so that they may be promptly resolved.

Respectfully submitted,

Dated: 7 May 2007 By: 

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